HOGAN & HARTSON

L.L.P.

4326 '02 APR 26 P3:59

DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

April 26, 2002

VIA FACSIMILE (301-827-6776)
AND FIRST-CLASS MAIL

Advisory Committee for Pharmaceutical Science
c/o Kathleen Reedy
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: *Upcoming Meeting, Written Comments*

Dear Ms. Reedy:

We are writing to present the views of Abbott Laboratories (Abbott) on a matter scheduled for discussion at the upcoming meeting of the Food and Drug Administration's Advisory Committee for Pharmaceutical Science on May 7-8, 2002. *See* 67 FR 19577 (April 22, 2002).

Specifically, we wish to comment on the draft guidance document titled, "Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling" (October 2001) (*the "Food-Effect Guidance"*). We do not at this time expect to present oral comments during the meeting, but we do ask that the Committee carefully consider our written submission in the course of its deliberations.

As you know, the *Food-Effect Guidance* recognizes that foods and beverages often have a clinically significant effect on the bioavailability (BA) of an active drug ingredient or on the bioequivalence (BE) of two different formulations of the same active ingredient. *Food-Effect Guidance* at 2. A growing number of drug products now bear labeling that describes a significant food effect – a trend which

Abbott believes is good for patients. Food-effect labeling contributes to consistent and more accurate dosing and can help patients adopt a routine set of conditions under which they take their medicines.

Second, the *Food-Effect Guidance* recognizes the need for BE studies under fed conditions, particularly where the reference or "pioneer" product bears food-effect labeling. *Food-Effect Guidance* at 4. Food effects may be formulation-specific, and two different versions of the same drug may react differently in the presence of food. In fact, two products may react differently depending on the quantity or type of food used. *See, e.g.,* Advisory Committee for Pharmaceutical Science (Nov. 16, 2000), Transcript at 193 (discussing example of two products, each with the same active ingredient and dosage form, that had clinically significant BA differences depending upon whether the drugs were taken with chocolate milk, apple juice, or orange juice). For these reasons, the *Guidance* endorses the need for well-controlled and well-designed fed BE studies where the reference product has a noted food effect. *Food-Effect Guidance* at 3 (noting that the mechanism by which food may affect BA is often unknown and cannot be determined by physical inspection or *in vitro* study).

Abbott agrees and compliments the agency for recognizing these points. Abbott's concern, however, is that the agency has not gone far enough to address the variable BA seen by many drugs under different meal conditions. Nor has the agency taken steps to ensure that BE studies performed by applicants under abbreviated new drug applications (ANDAs) follow the same meal conditions used in the study of the reference drug product. Instead, the agency recommends only the use of a high-fat, high-calorie test meal "to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected." *Food-Effect Guidance* at 6.

For a product with a known sensitivity to food, the agency's approach in many instances is likely to mask or obliterate important formulation differences. The better approach, we suggest, is to require fed BE studies under the meal conditions suggested in the labeling or, if the labeling is not specific, under the meal conditions likely to be followed by patients who use the drug. Alternatively, the sponsor of a BE study should follow the meal conditions that were used to support the efficacy of the reference drug product. Patients on a low-fat diet who are instructed to take their medications with meals should be assured that a generic substitute will behave the same under low-fat conditions as the pioneer.

Finally, while the *Food-Effect Guidance* allows for the use of other test meals (*Food-Effect Guidance* at 7), the *Guidance* puts the decision within the discretion of the sponsor. It is the generic drug sponsor's choice, for example, to conduct a BE study with a test meal other than the maximum (50 percent fat) meal described in the *Guidance*. *Id.* Abbott disagrees with this approach. The *Guidance* must recommend the use of a test meal that closely reflects the labeled conditions of use or the conditions under which the reference drug was studied. In fact, by allowing the sponsor to select the test meal, FDA invites the real risk that the sponsor may use food selection to drive or optimize the showing of BE. *See, supra,* Transcript at 193-94.

In short, the agency's thinking on the need for fed BE studies is pointed in the right direction but, at this stage, is too general. For products that are food-sensitive, it may be impossible to know in advance whether the product will behave in a linear or predictable way under different meal conditions. Simply comparing two products under fasting and high-fat conditions may be insufficient – especially when the drug is labeled for use under low-fat or other dietary conditions. Food-effects are not "yes/no" propositions; far too little is known about food-effects for FDA to assume the use of one type of meal for all drug products.

* * *

For these reasons, we respectfully request that the Committee consider three related points:

- the need for fed BE studies under conditions other than the maximum (50% fat) meal described in the *Food-Effect Guidance;*
- the need for fed BE studies under the conditions of use recommended or described in the labeling; and
- the need for fed BE studies that follow the same study design used in the clinical testing of the pioneer product.

We greatly appreciate your attention to this issue and look forward to observing the Committee's deliberations on May 7 and 8, 2002.

Sincerely,

David M Fox by RPB

David M. Fox

DMF:bah

cc: FDA Docket No. 01D-0488